Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU022.0825	**NEUROMUSCULAR DRUGS** **RADICAVA®** (edaravone solution for injection) **RADICAVA ORS®** (edaravone oral suspension
Effective Date: 10/1/2025	**Review/Revised Date**: 08/17, 09/17, 07/18, 07/19, 06/20, 07/21, 02/22 07/22, 07/23, 07/24, 07/25 JWL
Original Effective Date: 09/17	**P&T Committee Meeting Date**: 09/17, 10/17, 08/18, 08//19, 08/20, 08/21, 04/22, 08/23, 08/24, 08/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy, all the following criteria (a-d) must be met:
    a. Documentation of definite or probable amyotrophic lateral sclerosis (ALS) within the previous two years per the El Escorial (Airlie House) Criteria or the Awaji-Shima criteria (See Appendix 1)
    b. Documentation of baseline ALS Functional Rating Scale-Revised (ALSFRS-R) with at least two points in each individual item (See Appendix 2)
    c. Forced vital capacity (FVC) of at least 80% (taken within the past three months)
    d. Dosing is in accordance with the FDA approved labeling
2. For patients established on therapy:
    a. Documentation of a clinical benefit from therapy such as stabilization of disease or slowing of disease progression from pre-treatment baseline ALSFRS-R scores. Edaravone may not be covered for patients experiencing rapid deterioration while on therapy due to lack of clinical benefit in this patient population.
    b. Documentation that patient is not dependent on invasive ventilation or tracheostomy

c. Dosing is in accordance with the FDA approved labeling

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by, or in consultation with, a neurologist with expertise in ALS.

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
Radicava ORS®: 50 mL per 28 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Radicava® **(**edaravone) is a free radical and peroxynitrite scavenger that prevents oxidative damage to cell. Oxidative stress is considered to play a role in the onset as well as progression of amyotrophic lateral sclerosis (ALS) and edaravone may protect neuronal cells from oxidative stress. However, the exact mechanism by which it slows the decline of physical function in patients with ALS is unknown.

FDA APPROVED INDICATIONS:
Treatment of amyotrophic lateral sclerosis (ALS).

POSITION STATEMENT:

- The FDA's approval of edaravone was based on one small phase 3 placebo controlled trial in 137 Japanese patients with ALS. In this trial edaravone showed a smaller decline in ALSFRS-R score after 24 weeks compared with placebo [-5.01 ± 0.64 vs placebo -7.50 ± 0.66 (95% CI, 0.99 – 3.98, p = 0.0013]
- This trial had strict inclusion criteria based on Post hoc analysis of a subgroup of patients from a previous trial in a broader ALS population
    - Key inclusion criteria for this trial: age 20−75 years, definite or probable ALS according to the revised El Escorial criteria, ALS of grade 1 or 2 in the Japan ALS Severity Classification, Scores of at least 2 points on all 12 items of the (ALSFRS-R), Forced vital capacity of 80% or more, disease duration of two years or less, and a decrease of 1−4 points in the ALSFRS-R score during a 12-week observation period before randomization
        - Patients with Japanese ALS severity classification of class 5 were not included in the trial (only class/grade 1 or 2). Japanese ALS severity class 5 is using a tracheostomy tube, tube feeding, or tracheostomy positive pressure ventilation.
    - Key exclusion criteria for the trial: 3 or less on ALSFRS-R for dyspnea, orthopnea, or respiratory insufficiency
- Based on this trial, there is moderate quality evidence that edaravone may slow functional decline compared to placebo but only in a specific patient population with early, progressive disease, that has maintained function.
- Two prior clinical studies in a broader population of ALS patients (one with a wider inclusion criterion, and one with patients with more advanced disease) failed to reach statistical significance on their primary endpoints compared to placebo. Therefore, there is currently no evidence indicating that edaravone may be effective in slowing disease progression in a larger population of ALS patients who do not meet specific criteria.
- Riluzole is the second medication the FDA approved for the treatment of ALS and current standard of therapy along with supportive care. It has a relatively safe adverse effect profile and has been shown to prolong survival by about two months in patients with ALS. In the approval trial patients taking riluzole could continue receiving it throughout the study as long as the regimen remained unchanged and 91% of patients in the trial were on riluzole.
- Sodium phenylbutyrate/taurursodiol is the third drug approved for ALS. The exact mechanism of action is unknown; however, it is thought to target endoplasmic reticulum stress and mitochondrial dysfunction resulting in reduced neuronal death. The CENTAUR trial demonstrated a statistically significant treatment benefit, as measured by a slowing in decline on the ALSFRS-R, for sodium phenylbutyrate/taurursodiol compared to placebo. In post hoc long-term analyses, survival benefit was observed for those patients who were originally

randomized to sodium phenylbutyrate/taurursodiol compared to those originally randomized to placebo.

El Escorial (Airlie House) Criteria is used to help with diagnosis of ALS. It requires evidence of upper motor neuron degeneration by clinical, electrophysiological, or neuropathologic examination and lower motor neuron degeneration by clinical examination as well as progressive spread of symptoms. The Awaji algorithm maintains the general principles of the El Escorial/Airlie House criteria, but evaluates neurophysiological data in context of clinical findings, which allows for increased sensitivity and an earlier diagnosis of ALS.

REFERENCE/RESOURCES:

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9. Miller R, Mitchell J, Lyon M, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Amyotroph Lateral Scler Other Motor Neuron Disord. 2003; 4(3): 191-206.

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Costa J, Swash M, de Carvalho M. Awaji Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis: A Systematic Review. *Arch Neurol.* 2012;69(11):1410–1416**Appendix 1: Summary of Revised El Escorial Criteria and Awaji Criteria for ALS diagnosis[12]**

Diagnosis of ALS requires:

Revised El Escorial Criteria	**Awaji Criteria**
Evidence of LMN loss (reduced interferential pattern on full contraction and increased firing rate)	Evidence of LMN loss (reduced interferential pattern on full contraction and increased firing rate)
Evidence of reinnervation (motor units of large amplitude and longer duration)	Evidence of reinnervation (motor units of large amplitude and longer duration)
Fibrillation and sharp waves	Fibrillation and sharp waves or fasciculation potentials (fibrillation and sharp waves are required in weak limb muscles)
No. of Muscles Affected by Region: Cervical and lumbar-sacral region: a minimum of 2 muscles innervated by different roots and nerves Bulbar and thoracic region: a minimum of 1 muscle Diagnostic Classification: Awaji-Shima Cons	
Diagnostic Classification: **Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria:** **Clinically definite ALS** is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions or the presence of LMN and UMN signs in 3 spinal regions. **Clinically probable ALS** is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs. The revised El Escorial Criteria have an additional category “Probable ALS–Laboratory Supported,” which is defined when clinical signs of UMN and LMN dysfunction are found in only 1 region but electrophysiological signs of LMN loss are observed in 2 regions. **Clinically possible ALS** is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only 1 region or UMN signs are found alone in 2 regions or LMN signs are found rostral to UMN signs.	

Appendix 2: The ALS Functional Rating Scale — Revised (ALSFRS-R)

1) Speech: Score_____

- □ Normal speech processes **(4 points)**
- □ Detectable speech disturbance **(3 points)**
- □ Intelligible with repeating **(2 points)**
- □ Speech combined with non-vocal communication **(1 point)**
- □ Loss of useful speech **(0 points)**

2) Salivation: Score_____

- □ Normal **(4 points)**
- □ Slight but definite excess of saliva in mouth; may have nighttime drooling **(3 points)**
- □ Moderately excessive saliva; may have minimal drooling **(2 points)**
- □ Marked excess of saliva with some drooling **(1 point)**
- □ Marked drooling; requires constant tissue or handkerchief **(0 points)**

3) Swallowing: Score_____

- □ Normal eating habits **(4 points)**
- □ Early eating problems — occasional choking **(3 points)**
- □ Dietary consistency changes **(2 points)**
- □ Needs supplemental tube feeding **(1 point)**
- □ NPO (exclusively parenteral or enteral feeding) **(0 points)**

4) Handwriting: Score_____

- □ Normal **(4 points)**
- □ Slow or sloppy: all words are legible **(3 points)**
- □ Not all words are legible **(2 points)**
- □ Able to grip pen but unable to write **(1 point)**
- □ Unable to grip pen **(0 points)**

5) Cutting food and handling utensils: Score_____

a). Cutting food and handling utensils **(patients without gastrostomy)**

- □ Normal **(4 points)**
- □ Somewhat slow and clumsy, but no help needed **(3 points)**
- □ Can cut most foods, although clumsy and slow; some help needed **(2 points)**
- □ Food must be cut by someone, but can still feed slowly **(1 point)**
- □ Needs to be fed **(0 points)**

b). Cutting food and handling utensils (**alternate scale for patients with gastrostomy)**

- □ Normal **(4 points)**
- □ Clumsy but able to perform all manipulations independently **(3 points)**
- □ Some help needed with closures and fasteners **(2 points)**
- □ Provides minimal assistance to caregiver **(1 point)**
- □ Unable to perform any aspect of task **(0 points)**

6) Dressing and hygiene: Score_____

- □ Normal function **(4 points)**
- □ Independent and complete self-care with effort or decreased efficiency **(3 points)**
- □ Intermittent assistance or substitute methods **(2 points)**
- □ Needs attendant for self-care **(1 point)**
- □ Total dependence **(0 points)**

7) Turning in bed and adjusting bed clothes: Score_____

- □ Normal **(4 points)**
- □ Somewhat slow and clumsy, but no help needed **(3 points)**
- □ Can turn alone or adjust sheets, but with great difficulty **(2 points)**
- □ Can initiate, but not turn or adjust sheets alone **(1 point)**
- □ Helpless **(0 points)**

8) Walking: Score_____

- □ Normal **(4 points)**
- □ Early ambulation difficulties **(3 points)**
- □ Walks with assistance **(2 points)**
- □ Non-ambulatory functional movement **(1 point)**
- □ No purposeful leg movement **(0 points)**

9) Climbing stairs: Score_____

- □ Normal **(4 points)**
- □ Slow **(3 points)**
- □ Mild unsteadiness or fatigue **(2 points)**
- □ Needs assistance **(1 point)**
- □ Cannot do **(0 points)**

10) Dyspnea: Score_____

- □ None **(4 points)**
- □ Occurs when walking **(3 points)**
- □ Occurs with one or more of the following: eating, bathing, dressing (ADL) **(2 points)**
- □ Occurs at rest, difficulty breathing when either sitting or lying **(1 point)**
- □ Significant difficulty, considering using mechanical respiratory support **(0 points)**

11) Orthopnea: Score_____

- □ None **(4 points)**
- □ Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows **(3 points)**
- □ Needs extra pillows in order to sleep **(2 points)**
- □ Can only sleep sitting up **(1 point)**
- □ Unable to sleep **(0 points)**

12) Respiratory insufficiency: Score_____

- □ None **(4 points)**
- □ Intermittent use of BiPAP **(3 points)**
- □ Continuous use of BiPAP during the night **(2 points)**
- □ Continuous use of BiPAP during the night and day **(1 point)**
- □ Invasive mechanical ventilation by intubation or tracheostomy **(0 points)**

Total score: _____